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MEDLEN & CARROLL, LLP
101 HOWARD STREET
SUITE 350
SAN FRANCISCO, CA 94105

EXAMINER

FETTEROLF, BRANDON J

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PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114.

Applicant's submission filed on 3/05/2007 has been entered.

Claims 24-27, 29, 36, 84-86, 91-93 and 95 are currently pending.

Claims 84-86 and 91-93 are withdrawn from consideration as being drawn to a non-elected invention.

Claims 24-27, 29, 36 and 95 are currently under consideration.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 24-27, 29, 36 and 95 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of characterizing prostate cancer in a patient already diagnosed with prostate cancer by detecting the presence or absence of HIP1 in a biopsied tissue sample with a nucleic acid probe configured to hybridize to a HIP1 nucleic acid sequence consisting of the nucleic acid sequence of SEQ ID NO: 1, wherein the absence of HIP1 in said sample is indicative of PSA non-recurrence and/or recurrence free survival, does not reasonably provide enablement for a method of characterizing prostate cancer in a patient already diagnosed with prostate cancer by detecting the presence or absence of HIP1 in a sample with a nucleic acid probe configured to hybridize to a HIP1 nucleic acid sequence consisting of the nucleic acid sequence of SEQ ID NO: 1, wherein the absence of HIP1 is indicative the chance of PSA recurrence or chance of recurrence free survival. The specification does not enable any person skilled in the art to which

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it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir, 1988). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.'" (Wands, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the nature of the invention, (2) the relative skill of those in the art, (3) the breadth of the claims, (4) the amount or direction or guidance presented, (5) the presence or absence of working examples, (6) the quantity of experimentation necessary, (7) the state of the prior art, and (8) the predictability or unpredictability of the art.

Although the quantity of experimentation alone is not dispositive in a determination of whether the required experimentation is undue, this factor does play a central role. For example, a very limited quantity of experimentation may be undue in a fledgling art that is unpredictable where no guidance or working examples are provided in the specification and prior art, whereas the same amount of experimentation may not be undue when viewed in light of some guidance or a working example or the experimentation required is in a predictable established art. Conversely, a large quantity of experimentation would require a correspondingly greater quantum of guidance, predictability and skill in the art to overcome classification as undue experimentation. In Wands, the determination that undue experimentation was not required to make the claimed invention was based primarily on the nature of the art, and the probability that the required experimentation would result in successfully obtaining the claimed invention. (Wands, 8 USPQ2d 1406) Thus, a combination of factors which, when viewed together, would provide an artisan of ordinary skill in the art with an expectation of successfully obtaining the claimed invention with additional experimentation would preclude the classification of that experimentation as undue. A combination of Wands factors, which provide a very low likelihood of successfully obtaining the claimed

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invention with additional experimentation, however, would render the additional experimentation undue.

The nature of the invention

The claims are drawn to a method of characterizing prostate cancer in a subject diagnosed with prostate cancer comprising detecting the presence or absence of HIP1 with a nucleic acid probe configured to hybridize to a HIP1 nucleic acid sequence consisting of the nucleic acid sequence of SEQ ID NO: 1. The invention is in a class of invention which the CAFC has characterized as "the unpredictable arts such as chemistry and biology." *Mycogen Plant Sci., Inc. v. Monsanto Co.*, 243 F.3d 1316, 1330 (Fed. Cir. 2001).

Level of skill in the art

The level of skill in the art is deemed to be high, generally that of a PhD or MD.

The breadth of the claims

Applicants broadly claim a method of characterizing prostate cancer in a patient already diagnosed with prostate cancer by detecting the presence or absence of HIP1 in a sample with a nucleic acid probe configured to hybridize to a HIP1 nucleic acid sequence consisting of the nucleic acid sequence of SEQ ID NO: 1, wherein the absence of HIP1 is indicative of the chance of PSA recurrence and chance of recurrence free survival. Thus, the claims encompass the absence of HIP1 in any and/or all samples being indicative of the chance of PSA recurrence and/or chance of recurrence free survival which infers the "relative risk" of PSA recurrence and/or "relative risk" of cancer free survival (see for example, specification page 13, lines 9-11).

Guidance in the specification and Working Examples

The specification teaches (page 4, lines 9-12) that HIP1 may be utilized in a method for characterizing prostate tissue in a subject, wherein the presence or absence of HIP1 characterizes the tissue sample. For example, the specification teaches that HIP1 expression in individual patients reveals that there were progressively higher frequencies of HIP1 expression in benign, PIN, PCA and metastatic case. Conversely, there were progressively lower frequencies of the lack of HIP1 expression among the same (page 65, lines 25-28 and Figure 4a). Moreover, the specification

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teaches the clinical implications associated with HIP1 expression, wherein patients with tumors which did not stain for HIP1 expression did not develop a PSA recurrence (page 66, lines 5-11 and page 67, Table 1). For example, the specification teaches the following table which illustrates HIP1 expression and preoperative PSA as predictors of PSA recurrence (page 67, Table 1):

Significance	No PSA recur. (n,%)	PSA recur. (N,%)	Pearson's X2	Two-sided p
HIP1 Absent	14 (100%)	0 (0%)	4.034	0.045
HIP1 Expressed	77 (77%)	23 (23%)		
Preoperative PSA <4	22 (95.7%)	1 (4.3%)	4.482	0.034
Preoperative PSA >4	69 (75.8%)	22 (24.1%)		

In addition, the specification teaches that there is a survival advantage of PCa patients with tumors that had no HIP1 expression, wherein all patients that lacked HIP1 expression survived 67 months without evidence of recurrence as compared to 28% of the patients whose tumors expressed HIP1 died of prostate cancer (page 66, lines 17-26 and Figure 4b). Thus, while the specification teaches that in some instances there is a correlation between HIP1 expression in biopsied tissue samples and prostate cancer, the specification does not appear to provide a nexus between the absence of HIP1 in prostate tissues and the chance of PSA recurrence and or the chance of recurrence free survival. Moreover, the specification appears to be silent on the presence of HIP1 in any other sample, wherein the absence of HIP1 in said sample is indicative to the chance of PSA recurrence and or the chance of recurrence free survival.

Quantity of experimentation

The quantity of experimentation in the areas of cancer diagnosis and/or characterizing a particular stage of cancer is extremely large given that what may be "preferable" in the lab is only suggestive and does not qualify as a reasonable expectation of success, especially in a highly unpredictable art such as determining the chance, e.g., risk, of PSA recurrence or recurrence free survival.

The unpredictability of the art and the state of the prior art

The state of the art at the time of filing was such that one of skill could recognize that the expression of a cancer-associated nucleic acid molecule that appears to be 60% identical to the instantly claimed nucleic acid of SEQ ID NO: 1 has been found to be associated with colon cancer (see Chen et al. US 6,794,501, of record). With regards to HIP1 and/or a nucleic acid sequence consisting of SEQ ID NO: 1, the prior art appears to be silent an association of HIP1 and/or a nucleic acid consisting of SEQ ID NO: 1 and prostate cancer, and further, HIP1 being an identifier of a particular stage of prostate cancer.

It is noted, as stated above, that the specification teaches that in some instances there is a correlation between HIP1 expression and prostate cancer, the specification does not appear to provide a nexus between the absence of HIP1 in prostate tissues and the chance of PSA recurrence and or the chance of recurrence free survival. In other words, what may be "preferable" in the lab is only suggestive and does not qualify as a reasonable expectation of success, especially in a highly unpredictable art such as determining the stage of prostate cancer. For example, Tockman *et al* (Cancer Res., 1992, 52:2711s-2718s, of record) teach considerations necessary in bringing a cancer biomarker (intermediate end point marker) to successful clinical application. Although, the reference is drawn to biomarkers for early lung cancer detection, the basic principles taught are clearly applicable to other oncogenic disorders such as prostate cancer. Tockman *et al* teaches that prior to the successful application of newly described markers, research must validate the markers against acknowledged disease end points, establish quantitative criteria for marker presence/absence and confirm marker predictive value in prospective population trials (see abstract). Early stage markers of carcinogenesis have clear biological plausibility as markers of preclinical cancer and **if validated** (emphasis added) can be used for population screening (p. 2713s, col. 1). The reference further teaches that once selected, the sensitivity and specificity of the biomarker must be validated to a known (histology/cytology-confirmed) cancer outcome. The essential element of the validation of an early detection marker is the ability to test the marker on clinical material obtained from subjects monitored in advance of clinical cancer and *link* those marker results with subsequent histological confirmation of disease. This irrefutable link between antecedent marker and subsequent acknowledged disease is the essence of a valid intermediate end point marker (p. 2714,

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see Biomarker Validation against Acknowledged Disease End Points). Clearly, prior to the successful application of newly described markers, markers must be validated against acknowledged disease end points and the marker predictive value must be confirmed in prospective population trials (p. 2716s, col 2). In addition, Slamon et al. (Science Vol. 235, January 1987, pages 177-182, *of record*) teach other essential factors that are known to be important in the prognosis of breast cancer in individual patients such as size of the primary tumor, stage of the disease at diagnosis, hormonal receptor status, and number of axillary lymph nodes involved with disease (page 178, 1st column, 2nd paragraph). Such data are critical to assessing actuarial curves for relapse (Figure 3), and for comparing disease-free survival and overall survival to prognostic factors (Table 4).

Conclusion

Thus given the broad claims in an art whose nature is identified as unpredictable, the unpredictability of that art, the lack of guidance provided in the specification for correlation in vitro results to in vivo success, and the negative teachings in the prior art balanced only against the high skill level in the art, it is the position of the examiner that it would require undue experimentation for one of skill in the art to perform the method of the claim as written.

Note: In order to expedite prosecution, the Examiner would like to address Applicants arguments pertaining to the previous rejection of claims 24-27, 29, 36 and 95 under 112, 1st paragraph made in the Final Office Action as they relate to the instant rejection. In response to the previous rejection, Applicants assert that claim 24 has been amended to include elements of the absence of HIP1 being indicate of PSA recurrence or recurrence free survival. Thus, as stated by the Examiner, the specification is enabling for such a claim.

These arguments have been carefully considered, but are not found persuasive.

In response to Applicants arguments, the Examiner acknowledges that Applicants have amended claim 24 to include the limitation that the absence of HIP1 is indicative. However, the Examiner recognizes that Applicants have further amended the claims to recite “chance” of PSA recurrence or chance of recurrence free survival. As stated above, the Examiner recognizes that the recitation of “chance” infers a relative risk as defined in the specification on page 13, and the

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specification does not appear to provide a nexus between the risk of recurrence free survival or risk of PSA recurrence and the absence of HIP1 expression.

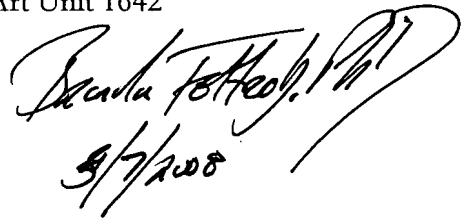
Therefore, No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brandon J. Fetterolf, PhD whose telephone number is (571)-272-2919. The examiner can normally be reached on Monday through Friday from 7:30 to 4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shanon Foley can be reached on 571-272-0898. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Brandon J Fetterolf, PhD
Patent Examiner
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